He travelled to the UK to print volumes of his book and then offered *Birds of America* to wealthy Britons. The copy now on sale was first bought by an early palaeobotanist, Henry Witham — 'subscriber number 11' — Audubon recorded. "I determined in an instant that this gentleman was a gentleman indeed ... we talked much, for I believe the good wine of Mr Witham had a most direct effect."

Only 119 complete copies of *Birds of America* are known to exist today and 108 of them are owned by museums, libraries and universities. And the value of the volume on sale is highlighted by the sale of a Shakespeare First Folio in the same auction estimated at £1–1.5 million.

Only 119 complete copies of *Birds of America* are known to exist today and 108 of them are owned by museums, libraries and universities.

Audubon was born in 1785 and was not the first person to paint all the birds of America. But his key work, including 435 life-size prints soon dominated the market.

He was born in the now Haiti but grew up in France. At the age of 18 he was sent to America, in part to escape conscription into Napoleon's army. He lived on a family-owned estate at Mill Grove near Philadelphia, where he hunted and studied art.

His last print was issued in 1838, by which time he had achieved fame but he travelled the country several more times in search of birds. He made one last trip in 1843, to form the basis for his final work on mammals, which was largely completed by his sons with the text written by his long-time friend, the Lutheran pastor John Bachman.

But it is his large-as-life volume on American birds by which he is most remembered and the rare volume on sale is likely to achieve record-breaking bids in Sotheby's in December.

Nigel Williams

Quick guides

Meiotic sex chromosome inactivation

Jeffrey M. Cloutier and James M.A. Turner

What is meiotic sex chromosome inactivation? Meiotic sex chromosome inactivation, commonly referred to as MSCI, is an epigenetic silencing process that occurs exclusively in germ cells, the specialized cells that undergo meiosis, to form sperm and eggs. In mammals, MSCI refers to the transcriptional silencing of genes on the X and Y sex chromosomes in the male germ cell, the spermatocyte. This process is mediated by a chromatin condensation event that packages the X and Y sex chromosomes into a compact structure, called the XY- or sex body (Figure 1). In this condensed state the genes on the X and Y chromosomes are inaccessible to the cell's transcriptional machinery, effectively causing chromosome-wide silencing.

How well conserved is it? MSCI has been described in many organisms, including eutherians and marsupials, chickens, nematodes and fruit flies. Despite the widespread conservation of MSCI, the precise timing and mechanism of silencing appears less well conserved, opening the possibility that MSCI may have arisen independently on numerous occasions throughout evolutionary history.

What triggers it? MSCI appears to be a consequence of having unequal sex chromosomes. In mammals, the X and Y sex chromosomes are highly divergent in structure and gene content, and it is this lack of homology that leads to MSCI. During prophase I of meiosis, maternal and paternal homologous chromosomes locate one another and gradually become tethered along their axes, culminating in complete pairing, or 'synapsis', at the pachytene stage (Figure 1). The X and Y chromosomes, however, can synapse only at a small distal region of homology; outside of this region, they remain unsynapsed. The unsynapsed regions induce MSCI, and as a result the associated genes are silenced. Experiments in mice and nematodes have shown that when either the X or Y chromosome is provided with a homologous pairing partner, it can form a synapsed bivalent that remains untouched by MSCI. This work has established sex chromosome asynapsis as the primary trigger of MSCI.

What is the consequence of MSCI? In a nutshell, X- and Y-linked gene silencing. Traditionally, MSCI was thought of as a transient meiotic

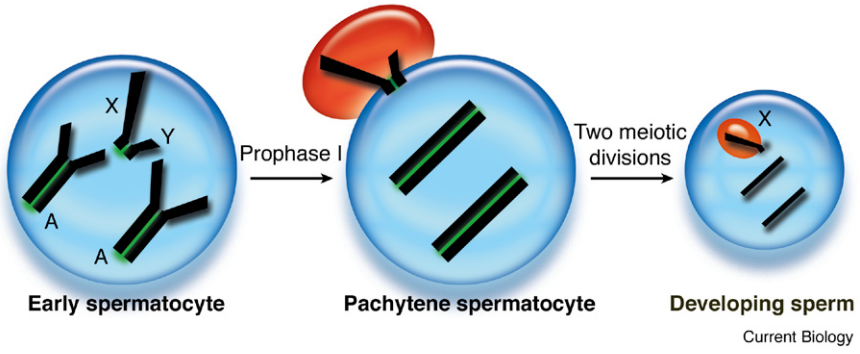

Figure 1. Meiotic sex chromosome inactivation.
In the early spermatocyte, homologous chromosomes (black) begin to synapse (shown in green). At this stage, the autosomes (A) and the X and Y chromosomes are transcriptionally active. In the pachytene spermatocyte, autosomes are fully synapsed and transcriptionally active. By contrast, the X and Y chromosomes are synapsed only at a small region of homology. The unsynapsed regions are subject to MSCI, leading to X and Y gene silencing and formation of the sex body (red). In the developing sperm (X-bearing cell depicted), the X chromosome is transcriptionally repressed (orange), with some genes reactivating.

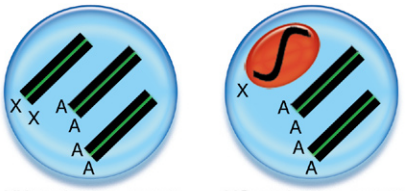

Figure 2. Meiotic silencing of unsynapsed chromatin in females.
In mammals, the XX pachytene oocyte has homologous chromosomes (black) that synapse completely (shown in green). In these oocytes, meiotic silencing does not take place and the autosomes (A) and two X chromosomes are transcriptionally active. In XO mouse pachytene oocytes, however, the single unsynapsed X chromosome triggers MSUC, leading to X chromosome silencing (shown in red).

phenomenon. It is now clear that it is maintained, although not completely, well beyond meiosis and into sperm development. In nematodes, the repressive effects of MSCI last even longer, imposing a chromatin imprint on the X chromosome that is heritable.

How is MSCI carried out? MSCI is regulated by specialized proteins and modifications that together establish a unique chromatin structure. In mammals, recognition of the unsynapsed X chromosome requires components of the chromosome synaptonemal complex, including SCP3, and members of the DNA-damage recognition and repair pathways, such as the tumor suppressor protein BRCA1. The act of silencing itself is dependent upon phosphorylation of histone H2AFX. Other modifications, including histone H2A ubiquitination by UBR2, methylation of histone H3 and replacement of histone H3 variants H3.1/H3.2 with H3.3, reconfigure and stabilize the chromatin in a compact state that is incompatible with transcription. In nematodes, silencing also involves specific components of the RNA interference pathway; in mammals, however, their role is less clear.

How does MSCI shape the X chromosome? Over the course of mammalian evolution, MSCI has made the X chromosome an unfavorable place to evolve genes necessary for meiosis and sperm development. Work has demonstrated that these sorts of genes are under-represented on the X chromosome in mice, nematodes and fruit flies. There are, however, important exceptions: testis-expressed microRNA (miRNA) genes are over-represented on the mouse X chromosome and many of these are transcribed during meiosis in spite of MSCI. These escapee miRNAs may have important functions in meiosis or even in regulating MSCI itself, but exactly how they evade silencing is a mystery. Amplification may represent another strategy by which genes can escape the repressive effects of MSCI; recent work has found that the mouse X chromosome is highly enriched in multiple copy genes, most of which are expressed during sperm differentiation. These genes dominate the X chromosome, accounting for 18% of the total X-linked protein-coding gene content.

What is MSUC and how is it related to MSCI? Recently it was discovered that meiotic silencing is not particular to the X and Y chromosomes: if autosomes remain unsynapsed at the pachytene stage, they are also subject to silencing. This more general silencing event was christened 'meiotic silencing of unsynapsed chromatin' (MSUC), and MSCI was thereafter acknowledged as an example of MSUC specifically affecting the sex chromosomes.

Can MSUC happen in females? Yes, MSUC is not specific to spermatogenesis. In chickens, the female is the heterogametic sex, carrying the Z and W sex chromosomes. New work has demonstrated that an MSUC-like response acts transiently on the Z and W chromosomes during chicken oogenesis. In female mammals, the two homologous X chromosomes synapse completely during meiosis and are transcriptionally active. However, in abnormal mouse oocytes, including those with synaptic defects or the wrong number of chromosomes, an MSUC response is mounted against any unsynapsed chromatin (Figure 2). The downstream consequence of silencing in oocytes is unknown, but in theory it would be deleterious, especially if crucial genes are switched off. While males have evolved mechanisms to tolerate sex chromosome silencing, this is not true for females, making silencing in the oocyte a potentially hazardous process. In the future, it will be important to understand how MSUC can impact female meiosis and fertility.

Why do MSCI and MSUC occur in the first place? This is unclear. An early idea was that MSCI is an adaptation to suppress genetic recombination between the non-homologous regions of the X and Y chromosomes, an event that could generate deleterious rearrangements. According to this theory, MSCI is merely a consequence of the heterochromatization event which in itself would prevent promiscuous recombination. It is also possible that the general form of meiotic silencing, MSUC, evolved initially as a quality control mechanism to selectively eliminate germ cells with synaptic defects. Under this model, MSCI would then have naturally surfaced when a pair of ancestral homologous autosomes gradually degenerated to form the X and Y chromosomes. Recently, it was also speculated that MSCI may exist to halt transcription from templates harboring DNA damage, such as the unsynapsed regions of the X–Y pair. This is all still work in progress.

Do we need it? Yes, it appears so. MSCI is clearly necessary for successful progression through male meiosis. Mutant mice with defects in MSCI are infertile, suffering a strict meiotic arrest in prophase I. This arrest could be the result of the illegitimate expression of 'meiotic-lethal' sex-linked genes at the pachtyene stage of meiosis, although this awaits formal proof.

Where can I find out more?

Burgoyne, P.S., Mahadevaiah, S.K., and Turner, J.M. (2009). The consequences of asynapsis for mammalian meiosis. Nat. Rev. Genet. *10*, 207–216.

Inagaki, A., Schoenmakers, S., and Baarends, W.M. (2010). DNA double strand break repair, chromosome synapsis and transcriptional silencing in meiosis. Epigenetics *5*, 255–266.

Turner, J.M. (2007). Meiotic sex chromosome inactivation. Development *134*, 1823–1831.

Yan, W., and McCarrey, J.R. (2009). Sex chromosome inactivation in the male. Epigenetics *4*, 452–456.

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